The problem of risk assessment and prophylaxis of venous thromboembolism in pregnancy

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In 1856 Rudolf Virchow described his classic triad of stasis, hypercoagulability, and vascular trauma as the cause of venous thromboembolism (VTE). From an obstetrician’s point of view he must have thought of pregnancy.

Pregnancy is associated with increased concentrations of coagulation factors (I, VII, VIII, IX, X, XI and XII), increased resistance to activated protein C, and decreased concentrations of protein S and antithrombin. Fibrinolytic inhibitors, such as plasminogen activator inhibitor type-1 (PAI-1) and inhibitor type-2 (PAI-2), derived from the placenta, increase as well (1). In addition, stasis, generated by the gravid uterus compressing venous flow from the lower limbs, is the most constant predisposing factor for VTE. Furthermore, vascular trauma may occur during delivery, particularly following caesarean section or vaginal operative delivery. These are the reasons, why in pregnancy the risk of VTE is three- to five-fold higher than in a nonpregnant woman of similar age (2, 3). The risk of thrombosis increases even further if a patient has certain concomitant genetic mutations. Most notably are polymorphisms in the genes for factor V (factor V Leiden) and prothrombin (G20210A), which account for a three- or respectively, twofold increase in pregnancy-related thrombosis (4).

Additional risk factors are age, smoking, varicose veins, obesity, prior VTE. Antiphospholipid syndrome, lupus erythematoses, heart disease and sickle cell disease are increasing the risk for VTE as well (5). Manifestations of maternal thromboembolic events include superficial and deep vein thrombosis, pulmonary embolism, ovarian vein thrombosis, and septic pelvic thrombophlebitis. VTE has become one of the leading causes of maternal morbidity and mortality in developed countries (6, 7). Nevertheless, incidence is low with one or two per 1,000 pregnancies (5, 8). Depending on which study is referred to, rates of pregnancy associated VTE rates are steady or rising (2, 9). Traditionally, the risk for thrombotic events has been considered greatest during the third trimester of pregnancy and immediately postpartum, but in the last two decades investigations suggested that the majority of the thromboembolisms occur antepartum (3, 8). One reason might be clinical practice of thromboprophylaxis during postpartum hospitalisation, where low-molecular-weight heparins are administered on a large scale.

The clinician dealing with the risk of VTE and thromboprophylaxis in pregnancy and postpartum faces at least three questions, which are difficult to answer! First, are pregnancy-related thromboembolic events preventable? Second, can clinicians identify the women who are at greatest risk (10)? Third, when is the best time to commence prophylactic anticoagulation? There are guidelines for the prophylaxis and treatment of thromboembolic events during pregnancy, labour and postpartum (11, 12). However, the recommendations made are based on case-control studies and expert opinions, none of them is based on evidence from randomized controlled trials or meta-analyses. This highlights the clinicians’ need for large-scale, high-quality studies, which establish the effectiveness of anticoagulation in pregnancy and postpartum and give us advice on the optimum prophylaxis and treatment strategy.

In this issue of *Thrombosis and Haemostasis*, Bauersachs et al. have made a successful attempt to partly fill this gap (13). Instead of conducting a randomized study, they performed a risk assessment with subsequent prophylaxis for women at increased risk of VTE due to prior thromboembolic events and thrombophilia status. With this approach of identifying patients at risk, a randomization would have been difficult to justify, but it has to be kept in mind that therefore, bias cannot be excluded.

At inclusion patients were assigned to one of three treatment groups according to their individual risk. High-risk and very high-risk patients were treated with different doses of dalteparin from enrolment, which resulted in a low level of symptomatic events. Patients assigned to the low-risk group were scheduled to clinical surveillance and dalteparin treatment postpartum or if additional risk factors occur. After all, 85.3% of these patients received thromboprophylaxis in the antepartum period, median treatment initiation was at 24 weeks. Consequently, it is little surprising that no thromboembolic events were recorded in this low-risk group. The effectiveness of the approach taken by the authors is beyond question, but that it might be less costly than blanket prophylaxis provision, as stated, has to be proven.
The safety assessment and pregnancy outcome shows a favourable pattern of the strategy used by Bauersachs et al. and makes it easy for clinicians to adopt in daily routine. Occurrence of clinically significant bleeding (4.6%) and congenital malformations (2.5%) corresponds to observations in Western-European collectives. Other adverse events, such as thrombocytopenia (2.2%; no cases with features of heparin-induced thrombocytopenia) and osteoporosis (0.1%) were infrequent, suggesting a favourable safety profile for dalteparin in pregnancy.

From the study of Bauersachs et al. we learn that in pregnancy as well as in the puerperium precise risk assessment including a profound patients history together with a risk-adjusted thromboprophylaxis is essential to minimize if not prevent thromboembolic events.

References